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UPON A NEW STYPTIC, AND UPON THE POSSIBILITY OF INCREASING THE COAGULABILITY OF THE BLOOD IN THE VESSELS IN CASES OF HÆMOPHILIA AND ANEURYSM AND INTERNAL HÆMORRHAGE.

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ONE of the most remarkable phenomena in the history of pathological and physiological science is the pause that frequently occurs between the discovery of a fact and its practical application. This divorce between knowledge and practice is in great part attributable to the fact that unfortunately physicians and surgeons are generally not practical physiologists, and still more unfortunately the physiologist is often not either a physician or a surgeon.

The history of the growth of the knowledge of the coagulation of the blood affords us with many instances of the truth of these remarks. If it had not been for such divorce between the knowledge of physiology and the knowledge of the requirements of practice, no doubt one of the first uses to which the discovery of fibrin ferment would have been put would have been its application as a styptic. I have, however, not come upon any evidence of its having been employed for such a purpose, and am therefore taking an opportunity here of suggesting such an application for it.

I have experimented somewhat extensively with a styptic of this nature and with a certain amount of success, but find that its coagulative properties can be greatly increased by availing ourselves of another fact in connection with the subject of coagulation, which has been for some considerable time in the possession of the physiologist. I refer to the influence which lime salts has been ascertained to exert upon the processes of coagulation (a fact the knowledge of which we owe among others to the researches of Hammarsten, Ringer, and Green) and also a fact to which particular attention has been recently directed by the brilliant discovery of Arthus and Pagès, that the shed blood can be kept permanently liquid by converting the lime salts in the blood into insoluble exalates by the addition of small quantities of any of the soluble salts of oxalic acid. In connection with our present purpose we have, however, merely to note that the coagulation of the blood can be hastened by the addition of calcium salts.

It is a fibrin-ferment solution to which 1 per cent. of $CaCl_2$ has been added, which I would therefore suggest for employment as a styptic, and it is with such a styptic that I have conducted my experiments. It may, perhaps, here be remarked in passing that the action of a styptic of this nature differs quite essentially from the action of such styptics as tannic acid, alcohol, the salts of the heavy metals, or the actual cautery, inasmuch as all these hæmostatics exert their effect indiscriminately upon whatever tissues they are brought in contact with, and inasmuch as their action consists in a coagulating or disintegrating effect, which entails the formation of eschars or, at any rate, subsequent inflammation. Quite in contrast with the action of these is therefore the action of a physiological styptic like the one here proposed. Such a styptic exerts an elective influence on the blood and is perfectly inert when brought in contact with other tissues, and is therefore perfectly painless in its action. Further, the coagulative influence which it exerts upon the blood probably takes place along the natural lines upon which normal blood coagulation occurs.

Experiments to determine the Efficacy of the Proposed Styptic.—With a styptic such as has been just described, I have, for instance, been able in the dog to cut across all the veins of the side of the head and neck with the exception of the common jugular, and to arrest the hæmorrhage by the application of the styptic without any ligatures. In a rabbit I found it possible to go even further. In an experiment directed to test the efficacy of the styptic I found it possible, by free application of the styptic, to cut across both common jugulars, both axillary veins, one lobe of the liver, and a number of mesenteric arteries without entailing the death of the animal from hæmorrhage. Further, in a large number of experiments in which I had occasion to cut across the central artery of the rabbit's ear in connection with a series of blood-corpuscle enumerations, I in every case suceeded in arresting the somewhat free hæmorrhage that occurs under such circumstances by the application of a drop or two of the above styptic on a piece of cotton-wool. Evidence of a more precise kind is, however, available, for it is evident that if we draw off a portion of blood from a vessel and divide it into two portions—one for a control and the other for an addition of styptic—we shall have an opportunity of obtaining quantitative expressions for the acceleration in coagulation thus produced. I will therefore here quote from my notebook a typical experiment in which the acceleration obtained by this means is clearly brought out.

Dog No. 1; October 12th, 1891. Chloroform and ether administered; 2.30 P.M., blood drawn off through a cannula in the carotid. Sample 1, drawn off 2.39 P.M., divided into two portions—*a* and *b*; *a*, Control, half solid at 2.43 P.M.; can invert tube 2.45 P.M.; time, six minutes. *b*, Three drops of styptic added to half a test-tube full of blood; can invert tube at 2.40 P.M.; time, one minute. Sample 2, drawn off 2.44 P.M. *a*, Control; still liquid at 2.45 P.M.; coagulation begun at 2.46 P.M.; can invert tube at 2.48 P.M.; time, four minutes. *b*, Two drops of styptic added; half solid at 2.45 P.M.; can invert tube at 2.46 P.M.; time, two minutes. Sample 3, drawn off at 2.49 P.M. *a*, Control still liquid at 2.50 P.M.; can evert 2.52 P.M.; time, three minutes. *b*, A few drops of styptic added to half a test tube of blood: can slope tube at 2.50 P.M., can evert at 2.51½ P.M.; time, one minute and a half; trachea clamped at 2.52 P.M., and clamp retained on trachea till dyspnœic respiratory efforts begin, when tracheal clamp is released. Sample 4. Dark venous blood, drawn off at 2.54½ P.M. *a*, Control, still liquid at 3 P.M.; coagulation begins at 3.2½ P.M.; can invert tube at 3.5 P.M.; time, ten minutes and a half. *b*, A few drops of styptic added; half solid at 2.56½ P.M.; can invert tube at 3 P.M.; time, 5½ minutes.

It will be seen that there is a marked acceleration produced by the styptic, in the coagulation of both arterial and venous blood. We have now to pass on to the preparation of the styptic. The source to which we have to go for our fibrin ferment is of course the coagulated blood, preferably the blood of the herbivora, and we can evidently most conveniently obtain it from the blood of either cattle or sheep. Of the two the blood of the former is to be preferred, because of its greater yield of fibrin ferment.

The fibrin ferment can naturally be obtained from either of the two elements of the coagulated blood, the clot and the serum. In practice the clot, or more strictly speaking the fibrin, is the most readily available source of fibrin ferment. It is for our purposes best obtained in the following manner. The blood is received from the vessels into three times its volume of ordinary water. It is then set aside for a few minutes until it commences to gelatinise, when it is stirred in the ordinary manner with a bundle of sticks or of wires. The fibrin that is collected in this manner from the diluted blood is composed of very much finer threads than that prepared from the undiluted blood, and it also presents the advantage of enclosing much fewer blood corpuscles. The fibrin thus obtained is washed out under a tap, or better in several changes, of ordinary water until it is practically free from blood pigment. This process of washing can usually be efficiently completed in the course of some ten minutes, and since the fibrin ferment is soluble in water it is expedient not to overdo the washing. The fibrin is now ready for use and the fibrin ferment is to be obtained from it by extraction with a moderate quantity of water, approximately some five to ten volumes of water may be used to each portion of fibrin. The extraction is to be continued for some hours (I have usually extracted for twenty-four hours). The filtered extract constitutes our fibrin ferment solution.[1] To this we add 1 per cent. of calcium chloride.

Instead of proceeding immediately to the extraction of the fibrin ferment it is preferable to keep the fibrin ferment for a few days at least under strong alcohol (it may be left there practically indefinitely without loss of its property of yielding fibrin ferment). In such cases the alcohol must naturally be removed by either washing or pressing between filter paper before proceeding to the extraction. If the extraction is now made with distilled water that has been boiled before using, there is evidently no difficulty in obtaining an aseptic fluid by this method. We have however quite a choice of means of accomplishing this purpose. We can filter through a Chamberland's filter, or we can add two volumes of 5 per cent. carbolic acid to one volume of the styptic without depriving it of its coagulative powers, if I may judge from a single experiment upon the subject in which the carbolic acid was added half an hour before experimenting with the styptic in extravascular plasma. Sterilisation by exposure to a moderate heat (*circ.* 60° C.) would probably also be practicable.

I have not yet been able to obtain anything like scientific evidence of the efficiency of this styptic in the cæse of bleeding in the human subject. In the case of a few accidental cuts such as are incidental to laboratory work, and in a few shaving cuts the styptic gave, as far as could be judged, satisfactory results. In the only case of which I have as yet learned in which it has been applied, in a case of serious hæmorrhage, it appears, when applied on a plug of cotton-wool, to have arrested the hæmorrhage when other means had failed. This was a case of hæmorrhage after supravaginal amputation of the cervix uteri, where, on account of the re-

[1] The efficacy of a fibrin ferment solution can be tested by means of a test plasma. The most readily available of these are the $MgSO_4$ plasma from the horse's blood, recommended by Schmidt, and the $MgSO_4$ plasma from the dog's blood, recommended by Wooldridge. These plasmas are obtained by receiving three volumes of blood into two volumes of a 20 per cent. $MgSO_4$ solution. The plasma is obtained either by filtration or by pipetting off the supernatant layers after the blood corpuscles have settled to the bottom. This plasma is diluted with eight to ten volumes of the fluid to be tested for fibrin ferment. The fluid to be tested must not contain calcium salts, as these alone will often inaugurate coagulation at any rate in Wooldridge's test plasma.

traction of the vessels, it was not possible to secure all the bleeding points. I am much indebted to Mr. Bowreman Jessett for his kindness in making a trial of the styptic in this case, and also for his permission to publish the fact here.

Possible Practical Applications.—It appears to me that in cases of epistaxis, a styptic such as I have here proposed might be found to be very useful, and that there are probably cases where it might also be useful in checking oozing in situations where ligatures cannot be successfully applied. It might also possibly prove of use in bleeding in hæmophilia. Further, in the case of troublesome bleeding after leech bite, we have every reason to hope that such a styptic would be effectual, since blood which has been kept liquid by leech extract is coagulable by the addition of fibrin ferment. With regard to a possibility of danger on absorption of the styptic into the vessels, I believe that no ill consequences would be associated with such a contingency. I have injected 20 c.c. of the styptic into the vessels of a rabbit without producing any intravascular coagulation.

Having thus far dealt with the subject of hastening the coagulation changes in shed blood, we have further to consider what the possibilities are in the way of increasing the coagulability of the blood within the vessels, and I propose before reporting the results of the experiments I have made upon this subject to glance briefly at the general question here involved.

With regard to this, we may say that *a priori* we should be prepared, from what is known of the salient facts of the coagulation of the blood, to expect that the coagulability of the blood within the vessels could be increased in three different methods: (1) by the injection of fibrin ferment; (2) by the injection of any substance which contributes to the organic substratum of fibrin, for example, of Wooldridge's tissue fibrinogen; and (3) by the administration or injection of calcium salts.

Injection of Fibrin Ferment.—With regard to the effect of injections of fibrin ferment, the facts have been ascertained for us, among others, by the researches of at least four of Alexander Schmidt's pupils. Three of these observers, Jabowicki,[2] Köhler,[3] and Birk[4], appear in no case whatever to have observed an increase of coagulability to result from fibrin ferment injections. On the contrary, they observed that the blood became more liquid and less coagulable after such injections, and they did not notice any other symptoms except this loss of coagulability and a rise of temperature to follow their injections. Another of Schmidt's pupils, Edelberg,[5] succeeded with "very strong fibrin ferment solutions" in producing intravascular coagulation in certain cases. On the other hand his fibrin ferment solutions contained up to 2.3 per cent. of proteids, and his experiments, therefore, cannot tell us anything about the fibrin ferment injections. On review of these facts, it will be evident that it would be entirely out of the question to use fibrin ferment injections as a means of increasing the coagulability of the blood intravascularly.

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[2] Quoted by Birk, Dissertation, Dorpat, 1880.
[3] Dissertation, Dorpat., 1877.
[4] Dissertation, Dorpat., 1880.
[5] *Arch. f. exp. Path.*, 1880.

Injection of Tissue Fibrinogen.—To Wooldridge belongs the honour of having demonstrated that the coagulability of the blood could be increased up to the point at which intravascular coagulation occurs by the injection of tissue fibrinogen into the blood, and Dr. Wooldridge was very anxious that this method of increasing the coagulability of the blood should be turned to some practical account in the treatment of aneurysm. In the further study which I have been able to give to the phenomena of the changes in the blood which are produced by injections of Wooldridge's tissue fibrinogen I have endeavoured to keep this object in view, but the difficulties seem to me to be still insuperable, as arterial blood—at least the normal arterial blood of a dog—refuses to clot with tissue fibrinogen intravascularly, and, further, even if it did clot, no method has yet been suggested by which the coagulation could be limited to the aneurysmal sac.[6] On the other hand, I have also succeeded in showing that tissue fibrinogen, when administered in smaller quantities than those which are sufficient to bring about immediate coagulation, becomes converted—or more probably disintegrated—in the blood into a substance—probably an albumose—which tends to produce abnormal liquidity of the arterial blood. It seems, therefore, to be unlikely that the blood could by such means be brought up to, and kept for prolonged periods at, such a condition of increased coagulability as one would desiderate for the gradual deposition of successive layers of fibrin upon the walls of an aneurysmal sac, and it will have to be kept in mind that, though Wooldridge's tissue fibrinogen does increase the coagulability of the blood more than it is possible to increase it by any other method, yet such increased coagulability is a very transient phenomenon in arterial blood, and very soon gives place there to an abnormal liquidity. In the venous system, on the other hand, or in arterial blood which has been rendered venous, Wooldridge's tissue fibrinogen readily increases the coagulability of the blood to the point at which intravascular coagulation occurs; but if the quantity of tissue fibrinogen present is insufficient to produce immediate intravascular coagulation, the venous blood soon returns to its normal level of coagulability. It would therefore appear that there will always be in the case of the injection of tissue fibrinogen a danger of doing too much in the direction of increasing the coagulability of the blood, and thus killing the patient by venous thrombosis, or, on the other hand, a danger of doing too little in this direction, and, as a consequence, rendering his blood less coagulable than it was previously.

Administration or Injection of Calcium Salts.—In the case of the calcium salts we appear, as far as my experiments enable me to judge, not to have any such Scylla and Charybdis to avoid as in the case of tissue-fibrinogen injections; for I have not observed any intravascular coagulation to result from injection of calcium salts directly into the blood, nor, on the other hand, any diminished liquidity to result from such administrations. On the contrary, I have in all cases observed a very considerable increase to follow the administration of calcium chloride either by the mouth or by the method of intravenous injections. This increase of coagulability is well shown on the following protocols:

[6] In a paper on Wooldridge's Intravascular Coagulation, to appear in a forthcoming number of the *Proceedings* of the Royal Irish Academy.

Dog (*circ.* 6 kilogrammes) November 14th, 1891, 2.10 P.M., 2.5 grammes of calcium chloride in 100 c.c. of water administered through an œsophageal tube, and chloroform and ether administered immediately afterwards. A cannula inserted into the carotid, and samples of blood withdrawn at the following intervals in order to test the condition of coagulability of the blood :—2.14 P.M., sample 1, can invert tube at 2.16 P.M. ; time, two minutes. 2.21 P.M., sample 2, can invert tube at 2.22½ P.M. ; time, one minute and a half. 2.40 P.M., sample 3, can invert tube at 2.41 P.M. ; time, one minute. 2.55 P.M., sample 4 ; time, forty-five seconds. 3.12 P.M., sample 5 : time, forty-five seconds. 3.15 P.M. ran into jugular 50 c.c of a 1.25 per cent. $CaCl_2$ solution. All the vessels of one side of the neck (with the exception of the great veins) are now cut across. The blood coagulates as it escapes from the vessels, and, instead of dripping on to the table, forms a tough adherent sheeting of blood clot which covers the whole of the subjacent tissues, and completely arrests the hæmorrhage. The animal is now killed by giving an excess of chloroform. No intravascular clots ; stomach full of food.

Dog (*circ.* 6½ kilos.) November 9th, 1891, 2.30 P.M., 2 grammes of $CaCl_2$ administered as in previous experiment in 40 c.c. of water. Anæsthetised as before, and drew off samples of blood as before from the carotid. 2.45 P.M., can invert test tube at 2.49 P.M. ; time, four minutes. 2.51 P.M., can invert test tube at 2.53 P.M. ; time, two minutes. 3.5 P.M., can invert test tube at 3.7P.M. ; time two minutes. 3.36 P.M., can invert test tube at 3.37½ P.M. ; time, one minute and a quarter. Animal now unintentionally killed by running 20 c.c. of a 1 per cent. oxalate of potassium solution into the jugular vein. The blood collected after death from the portal vein clots firmly in three minutes, that obtained from the heart a few minutes afterwards clots firmly in two minutes after collection.

In the case of another experiment where a small dog (*circ.* 4 kilos.) had received 1.5 grammes of $CaCl_2$ by the mouth, the first sample of blood which was drawn off immediately afterwards did not set firmly for twelve minutes. The next sample, which was withdrawn half-an-hour afterwards, set firmly in one minute. The third sample, collected three quarters of an hour afterwards, clotted firmly in two minutes, and the sample collected one hour afterwards clotted in one minute and a quarter.

The above are the protocols of only three experiments out of a series of seven, in all of which the increase of coagulability was very well marked, and it seems to me beyond question that the increase of coagulability observed was due to the calcium administered. It cannot have been due that the later collected samples contained an admixture of stagnant or already coagulated blood, for the cannula was in all cases taken out of the artery, carefully washed, and reinserted before drawing off each fresh sample. Again, the increased coagulability observed was probably not due to either of two causes, which a reference to protocol of dog No. 1[7] will show to exert a marked influence upon the coagulability of the blood. The modifying influences referred to are (*a*) the effect of hæmorrhage and (*b*) the effect of alterations in gaseous composition upon the coagulability of the blood. The influence of hæmorrhage upon coagulability—first studied, I believe, by Vierordt—is well brought out on noting the increase of coagulability in the case of the control tubes (*a*) of Samples 1, 2, and 3 (*vide* protocol, *supra*). I sought to guard against any such hæmorrhagic increase of coagulability in the case of my experiments with calcium by withdrawing very small samples of blood instead of, as in protocol of dog No. 1, very large samples.

With regard to the second class of influences, the changes in gaseous composition, which are shown in the same protocol —sample 3 (*a*) with sample 4 (*a*)—to affect the coagulability of the blood, I sought in the calcium experiments to avoid this

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[7] Quoted above in connection with experiments with regard to the efficacy of the proposed styptic.

source of error by attending carefully to the respiration in each case before drawing of the sample of blood. I endeavoured by these precautions to avoid the fallacies with which the path is thickly strewn, and on consideration of these facts I do not apprehend that the explanation of the increased coagulability by the addition of calcium salts to the blood is seriously open to question, especially as we have not only the fact of the increased rapidity of coagulation to go upon, but also the fact of the great firmness of the blood clots obtained from blood after administration of lime salts. The blood clots obtained under such circumstances are so firm and tough that they will bear almost any ordinary violence without breaking; such a large disc-shaped clot as is formed by running a small quantity of blood into a quart beaker can be thrown into the air and caught again an indefinite number of times without either breaking up or even soiling the fingers. Again, in a case the protocol of which the limits on my space forbid my quoting here, I was able to diminish the increased coagulability obtained by injections of $CaCl_2$ by subsequent injection of a weak oxalate of potassium salt solution.

Suggestions as to the Practical Application of these Facts.—I believe that the facts communicated above are sufficient to justify me in putting forward the suggestion that it might be worth while administering calcium salts (preferably calcium chloride) in conditions where it is desired to increase the coagulability of the blood in man. Such treatment might, I think, be tried in cases of internal hæmorrhage, even in cases where the hæmorrhage is acute, for the study of the protocols given above will show that the effect of an administration of calcium chloride by the mouth makes itself felt upon the coagulability of the blood in the dog within a very few minutes of its administration. This method of treatment might therefore be practicable in the case of hæmorrhage from the intestinal canal in typhoid fever, where the calcium administered would probably act both locally as a styptic and also indirectly by increasing the coagulability of the blood in the vessels. Similarly it might be tried where *post-partum* hæmorrhage was threatened, or where it was actually occurring, or again in cases of placenta prævia. In such cases of sudden internal hæmorrhage of course very large doses would be indicated. If the dosage and the dilutions I have employed in dogs without producing either local gastric congestion or any general symptoms were transferred to man the doses would be approximately 4 drachms of calcium chloride to a pint of water; but smaller doses would probably suffice.

The same treatment would, it appears to me, be worth giving a trial to in the case of hæmophilia, where it seems at least possible that the blood may be deficient in calcium salts. Even if the deficiency in coagulating power should, however, in such cases depend upon a deficiency in the organic substratum of fibrin, or in a deficiency in the power of forming fibrin ferment, the administration of calcium salts might be expected to act at least as a palliative, since it increases the coagulability of almost every kind of extravascular plasma (for example, peptone, $MgSO_4$ and 10 per cent. NaCl plasma). In any case where an operation had to be contemplated in a hæmophilia patient, a course of calcium chloride might at least be tried. The same thing applies in such cases of aneurysm as cannot be treated surgically.

Possibly, also, a similar treatment might be undertaken in anticipation of certain surgical operations where it was important to avoid all possible hæmorrhage, or even perhaps, though the remark seems facetious, where one had to take one's chance of a bullet without having a surgeon conveniently to hand.

It must, however, be noted that the calcium chloride is excreted very rapidly through the kidneys so that the coagulability of the blood soon reverts to its normal level.